Supplementary

Table S1 FDA Approved Therapies for Metastatic Prostate Cancer with Trials, Benefits, and US Cost Associations

Therapy	Population treated	FDA approval year	Trials and benefits/U.S. FDA approval	Cost in the United States
Chemotherapy				
Docetaxel	mCRPC	2004	- FDA approval based on: TAX 327 phase III randomized trial - ~1,000 males with mCRPC randomized to either docetaxel or mitoxantrone - Docetaxel demonstrated improvement in survival and quality of life (35) - Updated survival data: median survival of 19.2 mos in docetaxel every 3-week arm *vs.* 16.3 mos in mitoxantrone arm - 18.6% of patients survived 3 years in the docetaxel every 3-week arm *vs.* 13.5% in mitoxantrone arm (36)	$223.97 for 1 cycle $2,239.79 for 10 cycles (dose 75mg/m^2 with BSA 1.87=140.25mg dose per cycle)
Cabazitaxel	mCRPC (after prior treatment with Docetaxel)	2010	- FDA approval based on randomized phase II trial - 755 men, with a median survival of 15.1 mos *vs.* 12.7 mos in patients in cabazitaxel *vs.* mitoxantrone group, HR for death of 0.70 (95% CI 0.59-0.83, P<0.0001) (37) - Later demonstrated to have comparable efficacy to docetaxel in first line chemotherapy setting in the FIRSTANA trial (38) - Found to have survival benefit in CARD trial: 255 mCRPC patients with prior docetaxel and either abiraterone or enzalutamide randomized to receive either cabazitaxel or the other next generation hormone therapy (abiraterone or enzalutamide) - Median OS of 13.6 *vs.* 11.0 mos favored cabazitaxel arm (HR for progressive or death 0.52; 95% CI 0.40-0.68; p=0.008) over a second next generation hormone therapy (39)	$9,109.21 for 1 cycle $91,092.13 for 10 cycles (dose 20mg/m^2 with BSA 1.87=37.4mg dose per cycle)
Radiopharmaceuticals				
Radium-223	Symptomatic management for mCRPC	2013	- FDA approval based on ALSYMPCA Trial - Phase III trial of ~900 males randomized to standard of care alone or standard of care with radium 223 and demonstrated improvement in median OS (14.9 *vs.* 11.3 mos, HR 0.70, 95% CI 0.58-0.83, P<0.001) (40)	$47,939.43 per dose
Lu-177-PSMA-617	PSMA positive mCRPC who have previously received treatment with androgen receptor inhibition and 1-2 taxane chemotherapy	2022	- FDA approval based on the VISION trial - Phase III trial of lutetium-177-PSMA-617 *vs.* standard of care therapies that were not chemotherapy, immunotherapy or radiopharmaceuticals - Demonstrated statistically significant improvement in radiographic PFS (8.7 mos *vs.* 3.4 mos, P<0.001) as well as OS (15.3 mos *vs.* 11.3 mos, P<0.001) compared to standard of care alone (41)	$29,871.48 per dose $179,228.88 per 6 treatments
Second-generation anti-androgens				
Abiraterone	mCRPC +/- prior chemotherapy or newly diagnosed castrate sensitive metastatic prostate cancer	2011, indication expanded in 2012 and further in 2018	- FDA approval for patients with mCRPC who received prior chemotherapy - study of nearly 1200 patients with metastatic castrate resistant prostate cancer (CRPC) after docetaxel randomized to abiraterone + prednisone *vs.* prednisone alone - improvement in median OS of 15.8 mos *vs.* 11.2 mos (HR 0.74, P<0.0001) (20) - Indication was expanded to patients pre-chemotherapy in 2012 - trial of >1000 chemotherapy naïve patients who were randomized to abiraterone + prednisone *vs.* placebo - significant benefit was seen in median OS in the Abiraterone group [34.7 mos *vs.* 30.3 mos (HR 0.81, 95% CI 0.70-0.93; P=0.0033)] despite the fact that 44% of patients in the placebo group ultimately received abiraterone/prednisone as crossover or subsequent line of therapy (42) - Indication was expanded once again in 2018 with the US FDA approval to include patients with newly diagnosed castrate sensitive metastatic prostate cancer (based on data demonstrating improvement in OS, radiographic PFS as well as pain progression) - In a subsequent follow up after a median of 53.3 mos of follow up, median OS in the abiraterone group was 53 mos (95% CI 48.2 – not reached), *vs.* 36.5 mos in placebo group (95% CI 33.5 – 40 mos) with HR of 0.66, P<0.0001) (34) - Similar benefit was seen in another phase III randomized trial with this therapy (43)	Low-Dose with low-fat meal (250mg daily) $2868.38 (cost for 1 month) Standard dose (1g daily) $11,473.53 (cost for 1 month)
Enzalutamide	mCRPC +/- prior chemotherapy or newly diagnosed metastatic castrate-sensitive prostate cancer (mCSPC)	2014, indication expanded in 2023	- Phase III study of 1199 men with mCRPC after prior chemotherapy randomized to enzalutamide or placebo -improved OS benefit compared to placebo in men with mCRPC after chemotherapy with median OS of 18.4 *vs.* 13.6 mos (HR 0.63, 95% CI 0.53-0.75; P<0.001) - PREVAIL: phase III trial of >1700 chemotherapy naïve men randomized to enzalutamide or placebo - median OS of 32.4 mos in enzalutamide group and 30.2 mos in placebo group (HR 0.71, 95% CI 0.60-0.84, P<0.001) -Study was discontinued at a planned interim analysis due to benefit of active treatment (44) -ENZAMET: 1125 men with mCSPC randomized to either standard of care hormone therapy alone or hormone therapy with enzalutamide - significant improvement in median overall survival which was consistent across all predefined subgroup, with 5-year survival of 57% in control group and 67% in enzalutamide group (45) -ARCHES: 1150 men, same population as above - similar results with significant improvement in radiographic disease progression or death with use of enzalutamide (HR 0.39, 95% CI 0.30-0.50; P<0.001) (46)	$15,101.59 (cost for 1 month)
Apalutamide	Newly diagnosed mCSPC with use of ADT	2018	- TITAN: phase III randomized double-blind study - median OS not reached in androgen deprivation therapy + apalutamide group versus 52.2 mos in the androgen deprivation + placebo group (HR =0.65, P<0.0001) - OS benefit was seen even in the setting of a crossover rate of nearly 40% from placebo to apalutamide (47)	$15,712.57 (cost for 1 month)
Darolutamide	mCSPC in combination with docetaxel and ADT	2022	- ARASENS: phase III study of 1306 patients diagnosed with mCSPC who were randomized to receive either darolutamide (300 mg oral twice daily) *vs.* placebo, in combination with docetaxel and androgen-deprivation therapy - Benefit of darolutamide in OS (primary endpoint) for the darolutamide cohort at 4 years (62.7% compared to placebo 50.4%) with lower risk of death in the darolutamide cohort by approximately 32% - Additional benefits of darolutamide in the secondary endpoints such as skeletal event-free survival (HR =0.61, P<0.001), time to castrate-resistant prostate cancer (HR =0.36, P<0.001), and time to initiation of subsequent systemic anti-neoplastic treatment (HR =0.39, P<0.001) (48)	$14,303.34 (cost for 1 month)
PARP inhibitors				
Olaparib	mCRPC with BRCA1/2 mutations in combination with abiraterone (regardless of prior hormone therapy or docetaxel administration)	2023	Much of the benefit has been driven by patients with mCRPC with BRCA1/2 mutations (49) -PROFOUND: phase III study compared oral olaparib to either abiraterone or enzalutamide in men with metastatic CRPC who had progressed on prior treatment with next-generation hormone agent and had alterations in specific genes - Cohort A of the study included ~250 males with BRCA1, BRCA2 or ATM alterations and demonstrated OS of 19.1 mos *vs.* 14.7 mos favoring olaparib (HR 0.69, 95% CI 0.50-0.97, P=0.02) (50) -PROpel: randomized phase II trial evaluating treatment of patients with mCRPC with either abiraterone-olaparib versus abiraterone-placebo demonstrated improved radiographic PFS with abiraterone-olaparib over abiraterone-placebo (HR =0.65, P=0.034) (51) - FDA approved combination of olaparib with abiraterone for treatment of patients with mCRPC with BRCA1/2 mutations (regardless of prior hormone therapy or docetaxel use) based on the results of this trial (51)	$17,249.78 (cost for 1 month)
Rucaparib	mCRPC with BRCA1/2 mutations after prior treatment with chemotherapy and new generation hormone therapy	2020	TRITON 2 Trial: Study of ~150 males with BRCA mutation which showed a radiographic PFS of 9 mos (95% CI 8.3-13.5 mos) (52) - FDA approval based on TRITON 2 study	$9,154.81 (cost for 1 month)
Talazoparib	mCRPC with HRR-mutation in combination with enzalutamide for patients not previously treated in the setting of CRPC	2023	TALAPRO-1: International phase II trial evaluated patients with mCRPC and HRR mutations who had received at least one talazoparib dose - Objective response rate following median follow-up of approximately 16 mos was 29.8% (53) TALAPRO-2: A randomized, double-blind, phase III trial evaluated patients with untreated mCRPC who received either enzalutamide and talazoparib or enzalutamide and placebo - Median radiographic PFS was not achieved (54)	$19,005.08 (cost for 1 month)
Niraparib	mCRPC with BRCA mutations in combination with abiraterone for patients who have not previously received therapy for mCRPC	2023	MAGNITUDE: randomized, double-blinded, phase II trial evaluated patients with HRR-mutated mCRPC who received treatment with either niraparib and abiraterone to placebo and abiraterone - For the niraparib cohort, radiographic PFS demonstrated improvement (16.5 mos >13.7 mos; HR =0.73, P=0.022) - In subgroup analysis, patients with non-BRCA HRR mutations did not demonstrate improvement in radiographic PFS (HR =0.99) (55) - Secondary analysis investigated an inverse probability censoring weighting analysis of OS in order to account for subsequent treatments, with results demonstrating potential OS benefit for niraparib combination therapy (HR =0.54, nominal P=0.0181) (56)	$19,753.25 (cost for 1 month)
Immunotherapy				
Sipuleucel-T	mCRPC	2010	- Phase III trial of >500 mCRPC patients with asymptomatic or minimally symptomatic disease were randomized to sipuleucel-T or placebo - Although no difference was seen in median time to disease progression, use of sipuleucel-T resulted in improvement of OS of 4.1 mos (25.8 *vs.* 21.7 mos) (57)	$65,929.95 (cost for 1 infusion) $209,789.95 (for 3 infusions)
PD-1 Directed Therapy	Tissue agnostic use for advanced solid tumors with high levels of microsatellite instability (MSI-H) or deficient MisMatch Repair (dMMR)	Accelerated approval 2017; full approval 2023	- Study of PD-1 inhibition ~250 males with docetaxel-refractory prostate cancer, with 5% response rate in patients with disease expressing PD-L1 and only 3% in patients with low PDL-1 expression (58) - Phase II KEYNOTE-158 study included 233 patients with high MSI/dMMR (27 noncolorectal tumor types of which 2.6% had prostate cancer) showed objective response rate 34% and medial overall survival 23.5 months (59)	$11,957.28 (1 cycle) $418,504.80 (35 cycles)

https://dx.doi.org/10.21037/tcr-23-2289

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